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BRIEF COMMUNICATION

Seizures and epilepsy in Sotos syndrome: Analysis of 19 Caucasian patients with long-term follow-up

***Francesco Nicita, †Martino Ruggieri, ‡Agata Polizzi, §Laura Mauceri, ¶Vincenzo Salpietro, ¶Silvana Briuglia, *Laura Papetti, *Fabiana Ursitti, **Salvatore Grosso, ††Luigi Tarani, ††Maria Segni, ‡‡Salvatore Savasta, §§Pasquale Parisi, ¶¶Alberto Verrotti, and *Alberto Spalice**

***Child Neurology Division, Department of Pediatrics, Policlinico Umberto I, Sapienza University of Rome, Roma, Italy; †Department of Formative Processes, University of Catania, Catania, Italy; ‡National Center for Rare Diseases, Superior Institute of Health, Rome, Italy; §Health Care Center for Obstetrics and Gynecology "Lucina," Catania, Italy; ¶Unit of Genetics and Immunology, Department of Pediatrics, University of Messina, Messina, Italy; **Department of Pediatrics, Gynecology, Obstetrics, and Reproductive Medicine, Pediatric Neurology Section, University of Siena, Siena, Italy; ††Department of Pediatrics, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; ‡‡Department of Pediatrics, University of Pavia, Pavia, Italy; §§Department of Pediatrics, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy; and ¶¶Department of Pediatrics, University of Chieti, Chieti, Italy**

Summary

Sotos syndrome (SS) is an overgrowth syndrome characterized by typical facial appearance, learning disability, and macrocephaly as cardinal diagnostic features. Febrile (FS) and afebrile seizures are reported in 9–50% of cases. There is no evidence that patients with SS and FS later develop epilepsy, and no studies have investigated the electroclinical features and the long-term outcome in epileptic SS patients. The authors report a series of 19 SS patients with FS and/or epilepsy during childhood and a long-term follow-up. More than half of FS evolved to epilepsy. Temporal lobe seizures were recorded in 40% of patients with SS. Seizures were easy to control with common antiepileptic drugs in almost all patients. A careful neurologic evaluation is useful for SS patients, since seizures are an important finding among people with this overgrowth syndrome.

KEY WORDS: Sotos syndrome, Seizures, Epilepsy, Cerebral gigantism, Overgrowth syndrome.

Sotos syndrome (SS) (OMIM #117550) is an autosomal dominant disease characterized by three cardinal features: distinctive facial appearance, learning disability, and overgrowth resulting in tall stature and macrocephaly. Typical facial features include high, broad forehead, frontotemporal sparse hairs, malar flushing, down-slanting palpebral fissures, and a pointed chin. In addition, a range of major and/or minor anomalies may occur, such as advanced bone age, neonatal problems, scoliosis, joint laxity, tumors, auditory/visual disturbances, and behavioral problems (Tatton-Brown et al., 2005).

SS is caused by mutations in or deletions of the nuclear receptor set domain containing protein 1 gene (*NSD1*), located at 5q35.2–q35.3 (Kurotaki et al., 2002; Douglas et al., 2005). More than 400 patients with SS have been reported (Fickie et al., 2011).

Most SS patients have nonprogressive neurologic dysfunction and brain anomalies. Neurologic disturbances associated with SS are hypotonia, feeding difficulties, clumsiness, poor coordination, delayed language and motor development, behavioral anomalies, and seizures. The degree of learning impairment is estimated to be extremely variable, although it is present in almost all patients (Tatton-Brown et al., 2005).

Several studies affirm that seizures may appear in about 15–50% of patients, and they are estimated to be febrile in half of cases (Tatton-Brown et al., 2005; Baujat & Cormier-Daire, 2007; Tatton-Brown & Rahman, 2007). A recent review of 21 SS adults described seizures as rare (9%) (Fickie et al., 2011). However, no data are available on whether patients with SS and febrile seizures (FS) later develop epilepsy, and no studies have investigated the electroclinical features and the long-term outcomes of epilepsy in these patients.

The aim of this study is to analyze the neurologic profile of 19 Caucasian patients with SS, with particular regard to epileptic phenotype and outcome.

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Address correspondence to Alberto Spalice, Child Neurology Division, Department of Pediatrics, Policlinico Umberto I, Sapienza University of Rome, Viale Regina Elena 324, 00161, Roma, Italy. E-mail: childneurology.sapienzaroma@live.it

Methods

This multicenter, retrospective study was carried out at the Division of Pediatric Neurology, Umberto I Hospital, Sapienza University, Rome, Italy. To be eligible for this study, patients had to have been clinically diagnosed with typical SS (e.g., presence of all the cardinal features in the same patient) (Tatton-Brown & Rahman, 2007) and had to present with at least one FS or afebrile seizure (AF). All the patients had to have undergone full neurologic examination, brain magnetic resonance imaging (MRI), electroencephalography (EEG) recording, and long-term clinical and EEG follow-up. Age at onset of seizures, seizure semiology, EEG characteristics, brain MRI findings, and therapy with antiepileptic drugs (AEDs) were analyzed for each case. Genetic analysis of exons 2–23 of the *NSD1* gene was performed in the reported patients by means of denaturing high performance liquid chromatography (HPLC; Transgenomics, Omaha, NE, U.S.A.), and direct sequencing of the chromatographic variant on 3130xl sequencer (Applied Biosystems, Foster City, CA, U.S.A.). Seizures were classified according to criteria of the International League Against Epilepsy (ILAE) (Engel, 2001). Written informed consent was obtained from parents or guardians of all recruited people.

Results

Data from 19 Caucasian patients (15 male, four female) were collected from a cohort of patients referred to eight Italian Pediatric Neurology Divisions. The mean age at time of first evaluation was of 5 years 2 months (range 4 months–15 years), and the mean age at time of last follow-up was of 11 years 2 months (range 6–20 years). Minimum follow-up period was of 5 years (range 5–19 years). Febrile and afebrile seizures were recorded in 11 and 15 patients, respectively; seven children with FS developed generalized and/or focal AF. Clinical, neurologic, neuroradiologic, and genetic features of the 19 patients are summarized in Table 1.

Discussion

Febrile seizures, infantile spasms, absence, tonic–clonic, and myoclonic seizures have been all associated with SS (Tatton-Brown & Rahman, 2007). Furthermore, a wide spectrum of behavioral and emotional disturbances may occur in SS patients, such as attention-deficit-hyperactivity disorder, aggressiveness, irritability, pyromania, social inhibition, psychosis, and autistic features (Mauceri et al., 2000; Tatton-Brown et al., 2005; de Boer et al., 2006). The patients with SS reported herein had FS and/or epilepsy. Mean age of onset of FS was consistently before the onset of epilepsy (1 year 6 months vs. 5 years 5 months). The 64% of SS patients with FS developed epilepsy, a much higher percentage if compared with patients with nonsyndromic FS (3–5%). We noticed that in some of the reported patients the diagnosis of SS was suspected only after they came to our attention for the first seizure, which was febrile in all cases. This may be related to the mild-to-moderate general and neurologic impairment of these patients in the first years of life, in which the typical cardinal features of SS had not aroused suspicion until that moment.

Generalized tonic–clonic seizures were the most frequent type among generalized AF, with a prevalence of 47%. Notably, the 40% of patients had temporal lobe seizures (TLS). Clinical symptomatology of TLS may include olfactory, gustatory, or auditory hallucinations, automatisms, fear, auras (e.g., abdominal aura) with/without behavioral arrest, déjà vu– or jamais vu–like sensations. In two patients, TLS presented with abdominal aura and bursts of aggressiveness, thus being initially confused with behavioral disorders. Ictal EEG recording allowed for the differential diagnosis between TLS and behavioral problems in these two patients (see legend of Fig. 1). Interictal EEG studies in patients with FS revealed normal background activity or anomalies fitting with the epileptic manifestations. Notably, anomalies in the temporal areas were recorded in a majority of patients with epilepsy at interictal EEG.

Seizures appeared easy to control with the common AEDs at standard doses, such as valproic acid, oxcarbamazepine, carbamazepine, lamotrigine, levetiracetam, topiramate. In this case series, monotherapy with valproic acid was the most frequent used treatment. In general, AED administration resulted in progressive reduction and disappearance of seizures. Recurrence of seizures required dose correction; only two patients needed polytherapy. At the time of last follow-up, 4 of 15 epileptic patients discontinued AED therapy (mean seizure-free period: 5 years; seizure-free period range 2–10 years); the other 11 patients still receive AEDs with good clinical control in all cases but one (patient with periventricular nodular heterotopia 0.

The pattern of brain abnormalities in SS suggest delayed or disturbed maturation, in particular of midline structures. In a study of 40 SS cases, ventricular anomalies (90%), enlargement of supratentorial extracerebral fluid spaces (70%), and anomalies of corpus callosum (64%) and other midline structures (40%) were the typical findings. Periventricular nodular heterotopias were reported in three patients (8%) (Schaefer et al., 1997). In the present series 17 patients had central nervous system anomalies, which were similar to the previous alterations described in children with SS. Periventricular nodular heterotopia was observed in one case (5%). In general, we found a lower incidence of midline brain anomalies compared with the series of Schaefer et al.

We cannot clarify the reason for the clinical and EEG involvement of temporal lobe in our patients, since no abnormalities were found in the temporal areas by MRI examination. Furthermore, studies on the role of the *NSD1* gene on the brain (or temporal lobe) development are missing,

Table 1. Summary of the 19 reported patients with SS

Cardinal Sotos syndrome features and genetic analysis			
Facial gestalt		NSD1 analysis	
Yes	19 (100%)	NSD1-mutated SS patients	14 (74%)
No	–	Non-NSD1-mutated SS patients	5 (26%)
Overgrowth with macrocephaly		Type of NSD1 point mutation	
Yes	19 (100%)	Missense	10 (71%)
No	–	Frameshift	4 (29%)
Learning disability			
Yes	19 (100%)		
No	–		
Seizures' features			
Seizures [Mean age of onset]			
Only febrile		4 (21%) [1 year 6 months]	
Only afebrile		8 (42%) [6 years 2 months]	
Febrile → Afebrile		7 (37%) [1 year 5 months → 4 years 9 months]	
Seizure type		EEG pattern	
Febrile (11 pts)		Febrile seizures	
Only simple	6 (55%)	Normal	4 (36%)
Only complex	1 (9%)	Diffuse anomalies (slow waves)	4 (36%)
Simple + complex	4 (36%)	Focal anomalies	
Afebrile (15 pts)		Centrotemporal area	3 (28%)
Only GTCS	5 (33%)	Afebrile seizures	
Only TLS	4 (27%)	Diffuse anomalies	1 (7%)
Only atonic seizures	2 (13%)	Focal anomalies	
Only frontal lobe epilepsy	1 (7%)	Frontotemporal area	5 (33%)
Only absence seizures	1 (7%)	Parietotemporooccipital area	9 (60%)
Multiple seizures type[a]	2 (13%)	Response to AED therapy	
Patients requiring AED therapy		Febrile seizures	3 (100%)
Febrile seizures	4 (36%)	Afebrile seizures	
Afebrile seizures	15 (100%)	Monotherapy	12 (87%)
		Polytherapy	1 (6.5%)
		Drug-resistant epilepsy	1 (6.5%)
Nonepileptic neurologic features and neuroimaging			
Congenital hypotonia		Developmental delay	
Yes	17 (89%)	Yes	19 (100%)
No	2 (11%)	No	–
Other neurologic signs/symptoms		Neuroimaging	
Behavioral disturbances[b]	9 (47%)	LV enlargement	14 (74%)
Poor coordination	4 (21%)	SAS enlargement	7 (37%)
Ocular anomalies[c]	2 (10%)	Periventricular leukomalacia	6 (32%)
Vasovagal syncope	1 (5%)	Cavum septum pellucidum	4 (21%)
Poor feeding	1 (5%)	Cavum vergae	4 (21%)
Neonatal seizures	1 (5%)	Thinning of the CC	3 (16%)
		VRS enlargement	2 (10%)
		Brain	2 (10%)
		Other anomalies[d]	1 (5%)

TLS, Temporal Lobe Seizures; GTCS, generalized tonic–clonic seizures; LV, lateral ventricles; SAS, subarachnoid spaces; VRS, Virchow Robin spaces; CC, corpus callosum.

[a]One patient had TLS + GTCS, one patient had TLS + GTCS + absence seizures.

[b]Behavioral disturbances included: attention deficit hyperactivity disorder, aggressiveness, poor social behavior, pyromania, tics, obsessive-compulsive disorders, temper tantrum.

[c]Ocular anomalies included: nystagmus, strabismus, optic disk pallor.

[d]Other anomalies included: dysplastic fornix, Chiari type II malformation, pineal gland cyst, subarachnoid cyst, and periventricular nodular heterotopia.

although it is known that the transcript of the *NSD1* gene is expressed in brain tissue (Favarelli, 2005).

Conclusions

This is the first study investigating the electroclinical features and the long-term follow-up of seizures in patients with SS. More than half of FS in these patients evolved to epilepsy. Generalized tonic–clonic seizures were the more frequent type of generalized seizures, whereas TLS were recorded in the 40% of SS with epilepsy in this series. Because patients with SS may have both behavior disorders and seizures such as TLS, and since TLS may be confused with some behavior disorders, ictal EEG recording may be

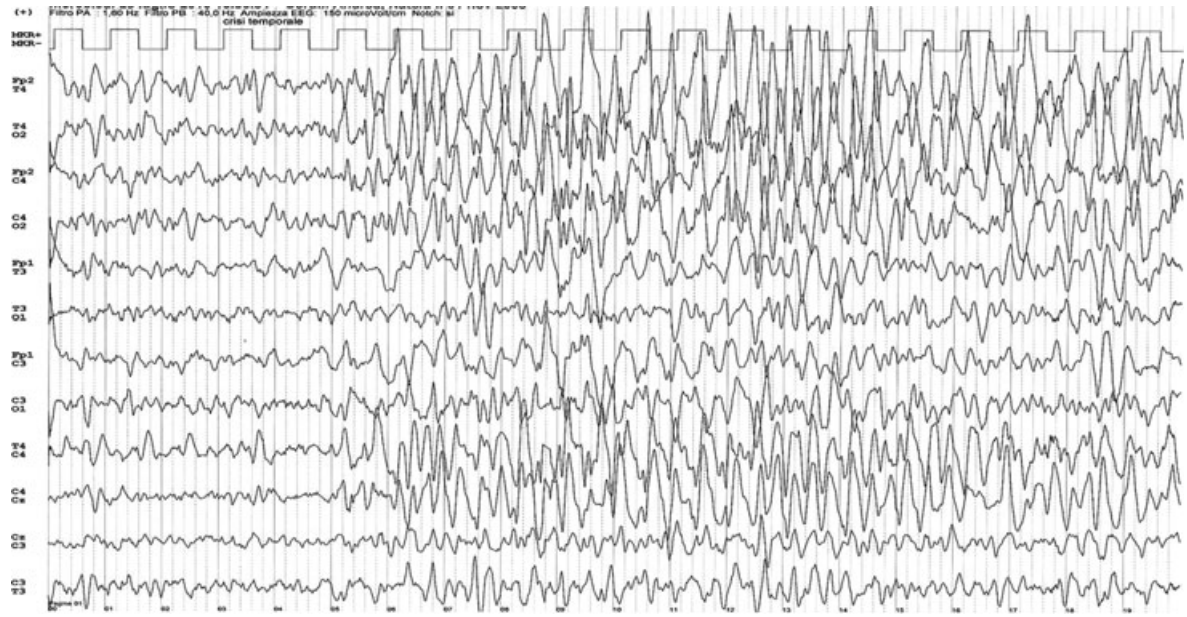

Figure 1.
Ictal EEG recording (20 s) of temporal lobe seizure in a 7-year-old boy with SS. Spikes start in the right temporal region (first 5 s), then high-voltage spikes and spike and waves complexes appear and remain for the duration of seizure in bilateral temporal areas (80 s). During seizure, the patient wanted to go home because he felt hungry and complained of stomachache, and manifested his feelings with a burst of aggressiveness. The patient did not lose consciousness. Parents reported numerous similar episodes, which were confused with behavior disturbances. Before the onset of temporal lobe seizures, the patient experienced FS and febrile status epilepticus, which presented with tonic–clonic seizures of the right side of the body and lasted 50 min at the age of 2 years.

helpful for differential diagnosis. Seizure control seems to be easy to obtain with monotherapy, or, less frequently, polytherapy with AED. A careful neurologic evaluation is useful in SS because seizures are an important finding among people with this overgrowth syndrome.

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Disclosures

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose.

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